DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

94811d

WARNING LETTER

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

JUL 2 2004

Thomas P. Kirkman
General Manager
BioDevelopment Associates, LLC
1805 – 136th Place NE, Suite 206
Bellevue, WA 98005

Dear Mr. Kirkman:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at BioDevelopment Associates, LLC. This letter also discusses your written response dated February 24, 2004, to the noted violations and requests that you implement prompt corrective actions. Carl Anderson, an investigator from FDA's Seattle District Office, conducted the inspection from November 3, through November 13, 2003. The purpose of the inspection was to determine whether the activities and procedures of BioDevelopment Associates, LLC, a testing facility, complied with Title 21, Code of Federal Regulations, (CFR), Part 58 – Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies. These regulations apply to nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by FDA.

Mr. Anderson reviewed both the records of your organization and personnel and the protocols for two nonclinical laboratory studies:

1. [redacted] in [redacted], " Protocol Number [redacted], sponsored by [redacted].

2. [redacted], " Protocol Number [redacted], sponsored by [redacted].

Our review of the inspection report prepared by the Seattle District Office revealed serious violations of the requirements of 21 CFR Part 58. At the close of the inspection, Mr. Anderson presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations in the presence of your Quality Assurance Manager, Dr. Sheridan Halbert.

This letter also acknowledges receipt of your letter dated February 24, 2004, addressed to Charles Breen. Your letter acknowledges each of the deviations listed below and offers corrective action. Proper implementation of these corrective actions should help to correct the deviations observed and prevent the recurrence of similar deviations in current and future studies. However, you have not provided the specific steps that you will take

to implement these corrective actions. The deviations noted on the FDA-483 and on our subsequent review of the inspection report, as well as the adequacy of your response, are discussed below.

1. Failure to assure that the Quality Assurance Unit (QAU) director has adequate education, training, or experience to perform his assigned functions [21 CFR 58.29(a)]

Any individual responsible for the supervision of a nonclinical laboratory study must have education, training, and experience to enable that person to perform his assigned functions. [21 CFR 58.29(a)]. You appointed a member of your management team to conduct the responsibilities of the QAU, but your documentation indicates that this person did not have the training and experience to assume these duties. Training records showed only — minutes of self training, — minutes of additional GLP training and — hours of unspecified previous job experience.

Your proposed corrective action should help to correct this deviation and prevent the recurrence of similar deviations in current and future studies. However, your response does not specify timeframes or specific courses of study for the QAU.

2. Failure to carry out the responsibilities of the Quality Assurance Unit (QAU) (21 CFR 58.35 (b))

The QAU did not adequately fulfill the responsibilities imposed by 21 CFR 58.35, which requires that the QAU assure management that the facilities, equipment, personnel, methods, practices, records and controls are in conformance with the regulations in 21 CFR part 58 (21 CFR 58.35(a). For example:

- The QAU did not assure conformance with the part 58 regulations, as required by 21 CFR 58.35(a), and did not inspect each study at intervals adequate to assure the integrity of the study, as required by 21 CFR 58.35(b)(6). For study ————, you used a contract laboratory, Phoenix Central Laboratory, to analyze hematology samples required by the study protocol. You did not inspect this facility or its portion of the study at all, and did nothing to determine whether it was conducting the study in compliance with applicable regulations, even though you were aware, prior to the initiation of the study, that this contract laboratory did not ordinarily operate under the GLP regulations.

- The QAU did not maintain a copy of a master schedule that contained all the data elements required by 21 CFR 58.35(b)(1). There were two master schedules, one for current studies and one for archived studies. The master schedule for archived studies did not contain the identity of the sponsor.

- The QAU did not did not determine that no deviations from approved protocols were made without proper authorization and documentation, as required by 21 CFR 58.35(b)(5). Specific examples of unauthorized protocol deviations are documented in sections 3, below.

- The QAU did not review the final study reports for studies [redacted] and [redacted] to assure the reported results accurately reflected these nonclinical studies, as required by 21 CFR 58.35(b)(6). Specific examples of omissions in the final report are described in section 4, below.

Your proposal to increase training for the QAU should help to correct the deviations observed and prevent the recurrence of similar deviations in current and future studies. However, your response does not specify timeframes or specific courses of study for the QAU. Likewise, your proposals with respect to the use of contract laboratories should help to correct that deviation and prevent future recurrence.

3. Failure to conduct nonclinical studies in accordance with the protocol (21 CFR 58.130(a)

The protocol for study [redacted] was not followed. For example:

- The protocol required an analysis for CBC with differential to be performed with regard to the test system, sheep. Instead of conducting this analysis as required by the protocol, you employed a contract facility, [redacted], that was not capable of performing this analysis on sheep blood and instead attempted to run the test on equipment calibrated for humans, generating results you knew to be invalid. Even though you were aware of this problem, you did not change to a laboratory capable of running the tests required by the protocol and did not submit a protocol amendment to eliminate the requirement to conduct these hematology analyses.

- Although the protocol required testing for Q fever, internal and external parasite checks, and vaccinations for *Clostridium* and *Pasteurella hemolytica* in the test systems, there was no documentation to establish that these requirements were met.

- Although the protocol required that deviation reports be signed by both the Study Director and the QAU, such reports were signed by the Study Director only.

Your proposed corrective actions should help to correct the deviations observed and prevent the recurrence of similar deviations in current and future studies. Specifically, your response regarding deviation reports should address our concerns if enacted.

4. Failure to prepare an adequate final report (21 CFR 58.185)

The final reports for study [redacted] and [redacted] did not contain all required information. For example:

- Neither final report references the location of reserve samples, as required by 21 CFR 58.185(a)(13).

- The final report for study [redacted] did not adequately address the stability of the test and control articles under the conditions of administration, as required by 21 CFR 58.185(a)(5) While the report stated that the test article was stabile, it did not indicate the basis for this conclusion, as there was no documentation that stability testing was performed and no alternative documentation of the stability of the test article.

- The final report for study [redacted] did not fully identify the composition and physical characteristics of the test article, as required by 58.185(a)(4), because it did not indicate which of the two types of test article materials (regular and soft) were used.

- The final report for study [redacted] did not include the signatures of either the study veterinarian or the principal investigator, who was the senior scientific representative of the animal facility you contracted with, as required by 58.185(a)(12).

Your proposed corrective actions should help to correct the deviations observed and prevent the recurrence of similar deviations in current and future studies. Your response partially disputes the observation regarding the necessary signatures for the final report for study [redacted] However, you conclude by acknowledging that these individuals were scientific professionals, they were included on the protocol, and you should have obtained the signatures. We agree that the regulations require the signatures of these scientists on the final report.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist at your facility. As a nonclinical testing facility, you are responsible for ensuring that you conduct nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for FDA-regulated products according to FDA regulations.

Within 15 working days after receiving this letter please provide written documentation of the steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any corrective action plan must include projected completion dates for each action to be accomplished. We wish to review the specific written procedures you have implemented or plan to implement, as well as training you have implemented or plan to implement for QAU personnel. Failure to respond and to implement appropriate corrective actions could result in enforcement action without further notice to you.

Please direct your response to the following address: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch LL (HFZ-312), 2094 Gaither Road, Rockville, Maryland, 20850, Attention Kevin Hopson.

A copy of this letter has been sent to FDA's Seattle District Office, 22201 – 23rd Drive S.E.. Bothell, WA 98021 and we request that you also send a copy of your response to that office. Please direct all questions regarding this matter to Mr. Hopson at (301) 594-4722, extension 128, or by e-mail at kevin.hopson @.fda.hhs.gov

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health